Supplementary Online Content

Shroff RT, Javle MM, Xiao L, et al. Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: a phase 2 clinical trial. *JAMA Oncol*. Published online April 18, 2019. doi:10.1001/jamaoncol.2019.0270

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Dose Reductions for Adverse Event Management

Dose Level	nab-Paclitaxel (mg/m^2)	Cisplatin (mg/m^2)	Gemcitabine (mg/m^2)
Baseline (0)	100	25	800
−1	75	25	600
−2	50	25	600
−3	50	20	600

eTable 2. Demographics and Baseline Disease Characteristics of Patients With Versus Those Without Progression-Free Survival Data

	With PFS Data (n = 58)	Without PFS Data (n = 2)	*P* Value
Mean age, years (SD)	58.1 (11.1)	69.0 (4.2)	0.17
Sex, n (%)			
Female	26 (45)	1 (50)	1.00
Male	32 (55)	1 (50)	
ECOG PS, n (%)			
0	22 (8)	0 (0)	0.53
1	36 (62)	2 (100)	
Tumor type, n (%)			
IHCC	36 (62)	2 (100)	1.00
EHCC	9 (16)	0 (0)	
GBC	13 (22)	0 (20)	
Disease stage, n (%)			
Metastatic	45 (78)	2 (100)	1.00
Locally advanced	13 (22)	0 (0)	
Baseline CA19-9, U/mL (IQR)	93 (15−590)	30938 (11764−50112)	0.03

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; IQR, interquartile range; PFS, progression-free survival; SD, standard deviation.

eTable 3. Demographics and Baseline Disease Characteristics of Patients With Versus Those Without Overall Survival Data

	With OS Data (n = 57)	Without OS Data (n = 3)	*P* Value
Mean age, years (SD)	58.2 (11.2)	62.3 (3.2)	0.53
Sex, n (%)			
Female	26 (46)	1 (33)	1.00
Male	31 (54)	2 (67)	
ECOG PS, n (%)			
0	22 (39)	0 (0)	1.00
1	35 (61)	3 (100)	
Tumor type, n (%)			
IHCC	35 (61)	3 (100)	0.73
EHCC	9 (16)	0 (0)	
GBC	13 (23)	0 (0)	
Disease stage, n (%)			
Metastatic	44 (78)	3 (100)	1.00
Locally advanced	13 (23)	0 (0)	
Baseline CA19-9, U/mL (IQR)	93 (15–590)	13350 (486–50 112)	0.02

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; IQR, interquartile range; OS, overall survival; SD, standard deviation.

eTable 4. Demographics and Baseline Disease Characteristics of Patients With Versus Those Without Treatment Response Data

	With Response Data (n = 51)	Without Response Data (n = 9)	*P* Value
Mean age, years (SD)	57.5 (11.0)	63.8 (9.5)	0.11
Sex, n (%)			
Female	22 (43)	5 (56)	0.72
Male	29 (57)	4 (44)	
ECOG PS, n (%)			
0	22 (43)	0 (0)	0.02
1	29 (57)	9 (100)	
Tumor type, n (%)			
IHCC	34 (67)	4 (44)	0.38
EHCC	7 (14)	2 (22)	
GBC	10 (20)	3 (33)	
Disease stage, n (%)			
Metastatic	40 (78)	7 (78)	1.00
Locally advanced	11 (22)	2 (22)	
Baseline CA19-9, U/mL (IQR)	93 (14–702)	184 (10–11 764)	0.84

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; IQR, interquartile range; OS, overall survival; SD, standard deviation.

eTable 5. Best Treatment Responses: Intention-to-Treat Analysis

Response, n (%)	All Patients (N = 60)	High Dose (n = 32)	Reduced Dose (n = 28)	IHCC (n = 38)	EHCC (n = 9)	GBC (n = 13)	Metastatic Disease (n = 47)	Locally Advanced Disease (n = 13)
DCR	43 (84)	25 (89)	18 (78)	29 (85)	6 (86)	8 (80)	32 (80)	11 (100)
CR	0	0	0	0	0	0	0	0
PR[a]	23 (45)	14 (50)	9 (39)	15 (44)	4 (57)	4 (40)	18 (45)	5 (45)
SD	20 (39)	11 (39)	9 (39)	14 (41)	2 (29)	4 (40)	14 (35)	6 (55)
PD	8 (16)	3 (11)	5 (22)	5 (15)	1 (14)	2 (20)	8 (20)	0
Unknown	9	4	5	4	2	3	7	2

Abbreviations: CR, complete response; DCR, disease control rate; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; ITT, intention-to-treat; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Includes both confirmed and unconfirmed responses.

eTable 6. Causes of Unresectability at Baseline in Patients who Underwent Surgery Following Treatment with Gemcitabine, Cisplatin, and nab-Paclitaxel

Patient Number	Tumor Type	Disease Stage	Cause of Unresectability at Baseline	Decision Maker
1	EHCC	Locally advanced	Regional lymph node metastasis	Surgeon
2	IHCC	Locally advanced	Tumor involvement of both lobes (tumor in segments II, III, and IV, and extending into the right lobe) Significant vascular invasion Suspected regional lymph node involvement	Surgeon
3	IHCC	Locally advanced	Tumor involvement of both lobes (tumor in segment IVB with satellite lesions in segments V and VIII) Regional lymph node metastasis	Oncologist
4	GBC	Metastatic	Regional lymph node metastasis Omental nodule	Oncologist
5	IHCC	Locally advanced	Tumor involvement of both lobes (large mass occupying the majority of the left lobe, with some extension into segment VIII and satellite lesion in segment V) Suspected regional lymph node involvement	Oncologist
6	IHCC	Locally advanced	Chronic liver disease with 24% future liver remnant volume	Surgeon
7	IHCC	Locally advanced	Tumor involvement of both lobes (segment IV and caudate) Suspicious peri-pancreatic lymph node	Surgeon
8	GBC	Metastatic	Suspected liver metastasis (liver tumor adjacent to the gallbladder, which had been resected prior to enrollment in the present trial) Suspected regional lymph node involvement	Surgeon
9	IHCC	Metastatic	Bilobar disease	Surgeon
10	IHCC	Metastatic	Distant lymphatic disease	Surgeon
11	IHCC	Metastatic	Extensive hepatic disease that would not permit adequate remnant post-resection Distant lymphatic disease	Surgeon
12	EHCC	Metastatic	Distant lymphatic disease	Surgeon

Abbreviations: EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma.

eTable 7. Treatment Exposure and Summary of Safety Profile of Gemcitabine, Cisplatin, and nab-Paclitaxel in the Safety Population

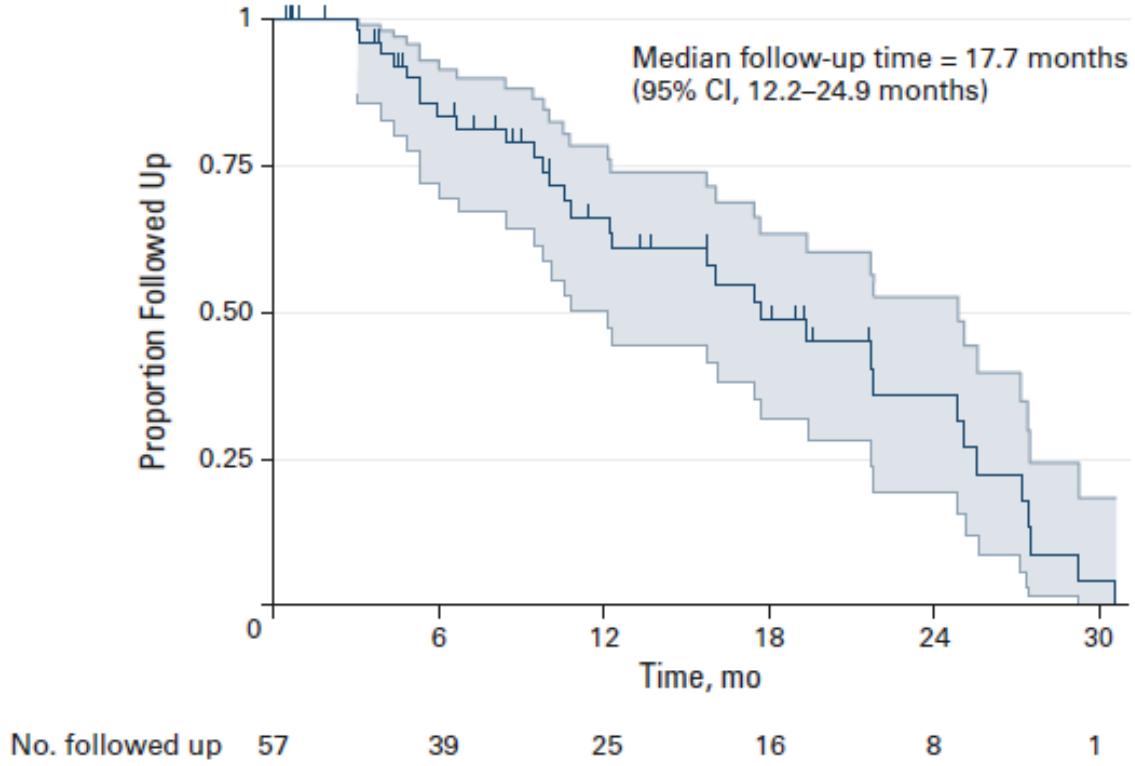
	All Patients (n = 57)	High Dose (n = 31)	Reduced Dose (n = 26)
Median treatment cycles, n (IQR)	6 (3-11)	8 (3-15)	5 (3-9)
Patients who remained on starting dose for duration of trial, n (%)	26 (46)	11 (35)	15 (58)
Premature withdrawal owing to AEs, n (%)	9 (16)	5 (16)	4 (15)
Discontinued cisplatin, n (%)	4 (7)	4 (13)	0
Discontinued nab-paclitaxel, n (%)	1 (2)	1 (3)	0
Any grade ≥3 AE, n[a] (%)	33 (58)	19 (61)	14 (54)
Grade ≥3 hematologic AEs, n[a] (%)			
Grade 3			
Neutropenia	17 (30)	8 (26)	9 (35)
Anemia	9 (16)	6 (19)	3 (12)
Thrombocytopenia	5 (9)	4 (13)	1 (4)
Febrile neutropenia	3 (5)	1 (3)	2 (8)
Grade 4			
Neutropenia	6 (11)	5 (16)	1 (4)
Thrombocytopenia	2 (4)	1 (3)	1 (4)
Grade 5	0	0	0
Grade ≥3 non-hematologic AEs, n[a] (%)			
Grade 3			
Diarrhea	2 (4)	1 (3)	1 (4)
Elevated ALP	2 (4)	1 (3)	1 (4)
Vomiting	2 (4)	2 (6)	0
Abdominal infection	1 (2)	0	1 (4)
Constipation	1 (2)	1 (3)	0
Cystitis	1 (2)	1 (3)	0
Elevated AST	1 (2)	1 (3)	0
Hypokalemia	1 (2)	0	1 (4)
Hyponatremia	1 (2)	1 (3)	0
Maculopapular rash	1 (2)	1 (3)	0
Nausea	1 (2)	1 (3)	0
Neuropathy	1 (2)	0	1 (4)
Sepsis	1 (2)	0	1 (4)
Thromboembolic event	1 (2)	1 (3)	0
Grade 4	0	0	0
Grade 5			
Sepsis	1 (2)	1 (3)	0

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; AST, aspartate aminotransferase; IQR, interquartile range.

[a] n = number of patients with ≥1 event, regardless of relationship to treatment.

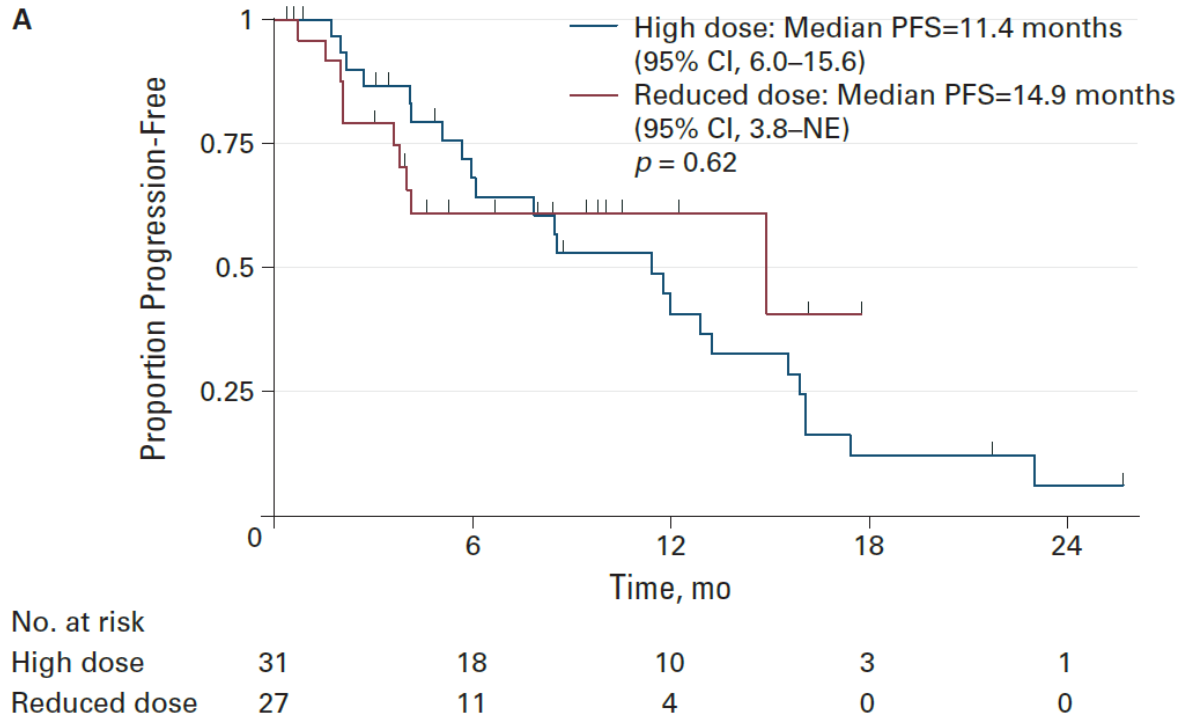
eFigure 1. Follow-up Among All Patients in the Intention-to-Treat Population for Whom Data Were Available (n = 57).

CI, confidence interval; mo, months.



eFigure 2. Progression-Free Survival Among All Patients in the Intention-to-Treat Population for Whom Data Were Available (n = 58): (A) By Dose Group; (B) By Tumor Type; (C) By Disease Stage.

CI, confidence interval; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; mo, months; NE, not estimable; PFS, progression-free survival.



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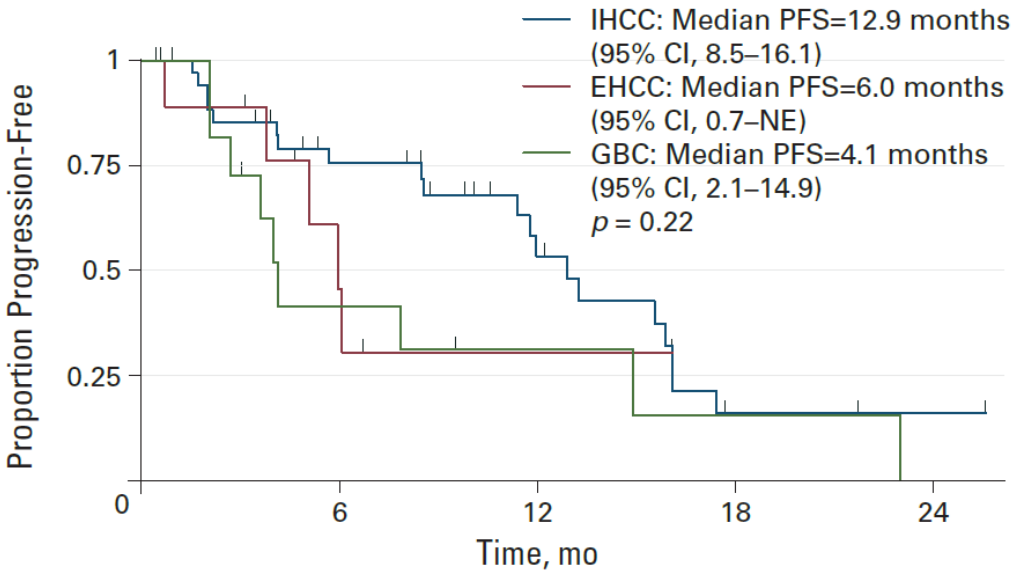
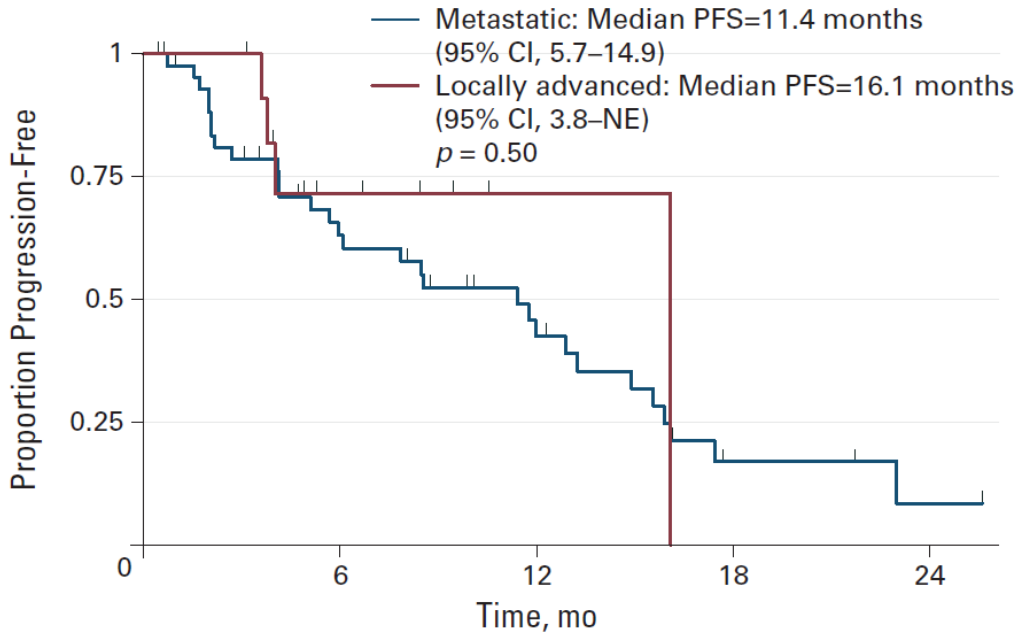


No. at risk					
IHCC	36	22	11	2	1
EHCC	9	3	1	0	0
GBC	13	4	2	1	0

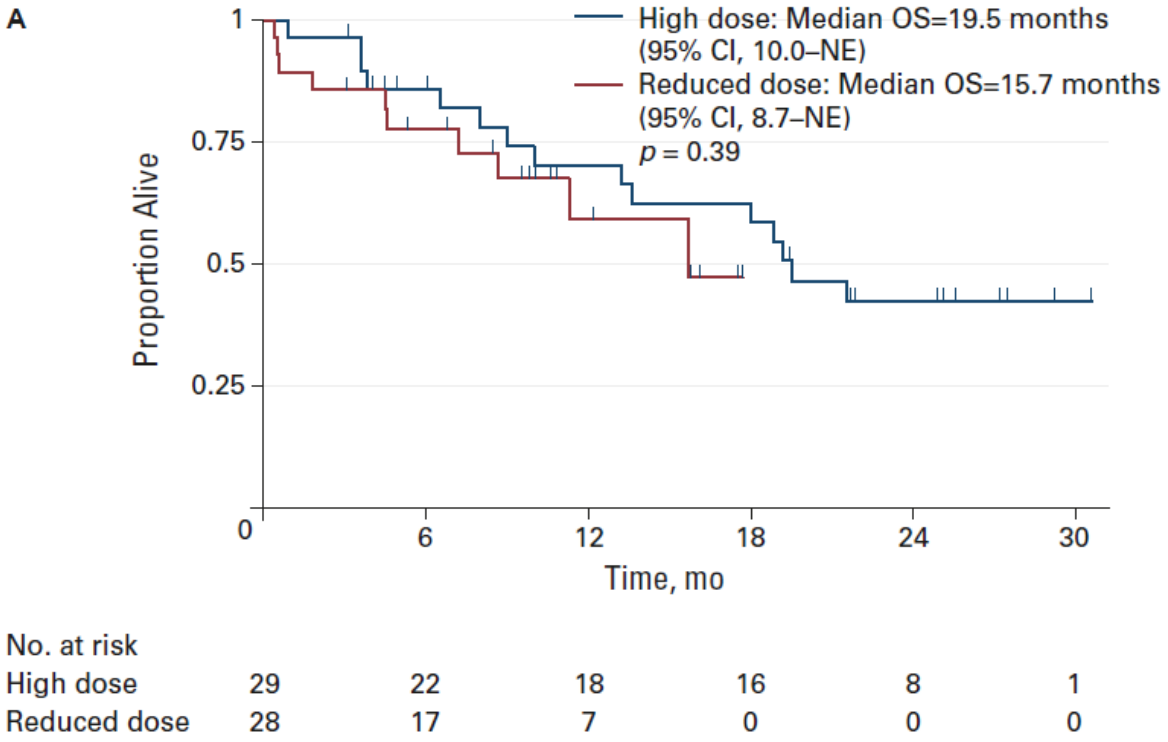
C



No. at risk					
Metastatic	45	24	13	3	1
Locally advanced	13	5	1	0	0

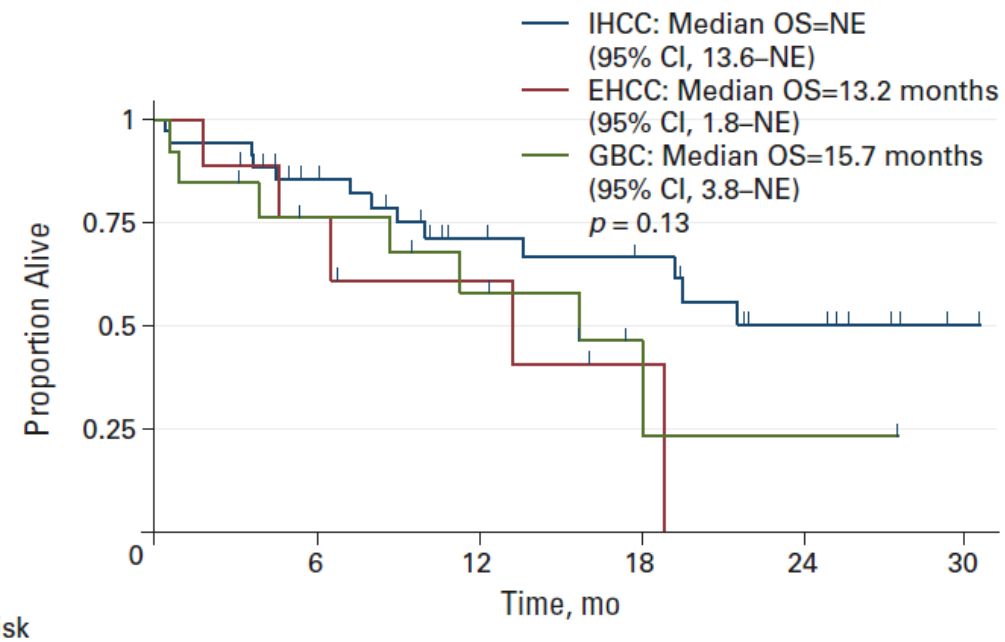
eFigure 3. Overall Survival Among All Patients in the Intention-to-Treat Population for Whom Data Were Available (n = 57): (A) By Dose Group; (B) By Tumor Type; (C) By Disease Stage.

CI, confidence interval; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC, intrahepatic cholangiocarcinoma; mo, months; NE, not estimable; OS, overall survival.



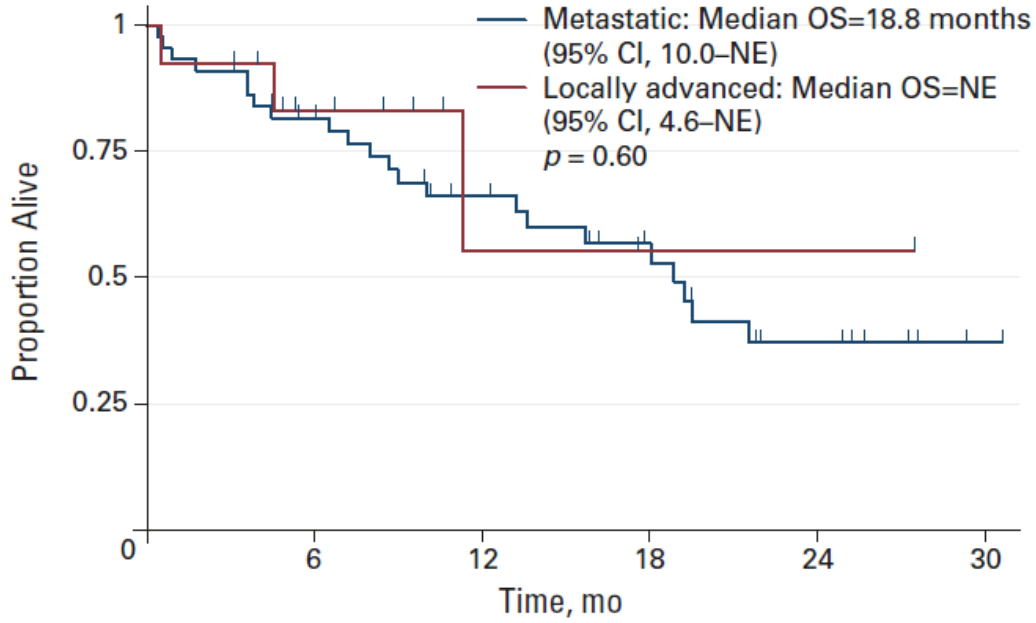
No. at risk						
High dose	29	22	18	16	8	1
Reduced dose	28	17	7	0	0	0

B



No. at risk						
IHCC	35	25	16	13	7	1
EHCC	9	5	3	1	0	0
GBC	13	9	6	2	1	0

c



No. at risk						
Metastatic	44	32	23	15	7	1
Locally advanced	13	7	2	1	1	0